

# **Latent tuberculosis infection screening and treatment in HIV: insights from evaluation of UK practice**

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## **Abstract**

Latent tuberculosis infection (LTBI) screening and treatment in HIV positive individuals in the UK is advocated by the British HIV Association (BHIVA) and NICE, although each recommends differing strategies. We undertook an evaluation of UK practice, relating the responses to the local HIV/TB disease burden. 162 of 188 (86%) UK geographical areas responded; only 93/162 (57.4%) offer LTBI testing with considerable heterogeneity in practice, and no difference in HIV/TB burden between areas offering testing and those who do not. Only 33/93 (35.5%) and 6/93 (6.5%) reported full compliance with BHIVA and NICE guidance respectively. A uniform national guideline is required.

## INTRODUCTION

HIV positive individuals are at an increased risk of acquiring tuberculosis (TB) and progressing to active disease through reactivation of latent TB infection (LTBI) (1). Analysis of the incident TB rate in the UK HIV positive cohort, demonstrates that there are high rates in Black Africans, those with a low blood CD4 count, and that rates are also higher in white individuals, than in the background HIV negative white population. This is despite access to, and widespread use of, anti-retroviral therapy (ARV) (2).

An increasing drive by the World Health Organization to identify and treat LTBI in HIV positive individuals as part of TB control (3,4), particularly in high HIV prevalence/low income settings, is supported by a Cochrane meta-analysis that found treating LTBI in this group reduced the risk of active TB by 32% (5). Since mortality from HIV/TB remains high in the UK (6), there are calls for expanded LTBI screening and treatment here (2).

Currently, LTBI screening in HIV positive individuals is advocated by the British HIV Association (BHIVA) (7) and the National Institute of Health and Care Excellence (NICE). The NICE guidance in place at the time of this evaluation was from 2011 (8). BHIVA recommend screening selected individuals with an interferon gamma release assay (IGRA), dependent upon a combination of criteria including the region of origin, duration of receipt of ARV and the CD4 count. NICE advocate screening all those with a CD4 count of 200 - 500 cells/ mm<sup>3</sup> with an IGRA plus the additional option of a tuberculin skin test (TST), with a definite recommendation of IGRA plus TST in those with CD4 <200 cells/mm<sup>3</sup>. Chemoprophylaxis is advocated by both if LTBI is diagnosed. Little is known about whether, and how, HIV healthcare providers implement these guidelines. A national evaluation of UK practice is therefore highly topical and

policy relevant with respect to understanding how screening is provided, the level of adherence to current guidance and whether the HIV/TB burden in different centres has any impact on practice.

## **METHODS**

### **Questionnaire design**

An online questionnaire was devised and one HIV professional working for each HIV healthcare provider organisation in the UK was invited to participate in the evaluation.

### **HIV prevalence and TB incidence data**

188 geographical areas in the UK were identified and had data available on HIV prevalence and TB incidence data.

Full details of the methods are available in the supplementary information.

## **RESULTS**

### **Response rate**

Responses were obtained from 116 individuals, representing 162 UK geographical areas, since some respondents provided HIV care for more than one geographical area. The overall response rate was therefore considered to be 162/188 (86%).

### **HIV and TB burden in all geographical areas**

There was no difference in HIV/TB burden between those geographical areas who did, and did not, respond to the survey ( $p=1.000$ ).

### **Size of HIV cohort in responding areas**

The total number of patients reported as being treated within their HIV centres by the 116 respondents was 73,395 (90% of total HIV cohort reported by PHE in 2014 (9)). The median was 300, range 10-8,000 and inter-quartile range 170-700.

### **Coverage of screening HIV positive patients for LTBI**

Only 93/162 (57.4%) of geographical areas reported offering any form of LTBI screening, with no difference in HIV/TB burden between the geographical areas who offered screening and those who did not ( $p=0.22$ ) (Table 1).

**Table 1. HIV/TB categories by LTBI screening**

HIV prevalence and TB incidence rate category	Offer screening n (%)	Do not offer screening n (%)
High HIV/High TB <sup>1</sup>	17 (18.3)	17 (24.6)
High HIV/Low TB <sup>2</sup>	8 (8.6)	3 (4.3)
Low HIV/High TB <sup>3</sup>	2 (2.2)	5 (7.2)
Low HIV/Low TB <sup>4</sup>	66 (71)	44 (63.8)
Total	93 (100)	69 (100)

**Footnotes**

<sup>1</sup>High HIV:  $>2/1,000$  HIV prevalence; High TB:  $>20/100,000$  TB incidence

<sup>2</sup>High HIV:  $>2/1,000$  HIV prevalence; Low TB:  $\leq 20/100,000$  TB incidence

<sup>3</sup>Low HIV:  $\leq 2/1,000$  HIV prevalence; High TB:  $>20/100,000$  TB incidence

<sup>4</sup>Low HIV:  $\leq 2/1,000$  HIV prevalence; Low TB:  $\leq 20/100,000$  TB incidence

## Selection of patients to screen for LTBI

Of the geographical areas offering any kind of LTBI screening, 57/93 (61.3%) reported using the current CD4 count as a screening criterion, with 53/57 (93%) screening adults with a CD4 count of  $\leq 200$  cells/mm<sup>3</sup> but decreasing numbers offering screening at higher CD4 counts (Table 2). 75/93 (80.6%) used the patient's country of origin, with all screening those from high TB incidence countries, but fewer than two thirds screening from any other region. The duration of receipt of ARV treatment was the least utilised criterion.

**Table 2. Criteria used to guide LTBI screening**

Screening criteria	n (%) Total n = 93 geographical areas offering screening	
<b><i>CD4 count criteria</i></b>	57	(61.3)
CD4 count $\leq 50$	53/57 <sup>1</sup>	(93)
CD4 count $\leq 100$	53/57 <sup>1</sup>	(93)
CD4 count $\leq 200$	53/57 <sup>1</sup>	(93)
CD4 count $\leq 350$	51/57	(89.5)
CD4 count $\leq 500$	45/57	(79)
CD4 count $> 500$	33/57	(57.9)
Other reported CD4 count criteria - Individual assessment	4/57	(7)
<b><i>Country of origin criteria</i></b>	75	(80.6)
High TB incidence country $> 40/100,000$ pop.	75/75	(100)
Medium TB incidence country 20-40/100,000 pop.	49/75	(65.3)
Low incidence TB country $< 20/100,000$ pop.	35/75	(46.7)
Other reported criteria – Eastern European countries	1/75	(1.3)
<b><i>Duration receiving ARV criteria</i></b>	52	(60)
Under 6 months	48/52	(92.3)
Under 1 year	42/52	(80.8)
Under 2 years	42/52	(80.8)
Other reported criteria – Individual assessment	4/52	(7.7)

Footnote

<sup>1</sup>53 centres offering screening to patients with a CD4 count of  $\leq 200$  are the same centres offering screening to those with CD4 counts in the  $\leq 100$  and  $\leq 50$  categories

### **LTBI screening tests**

IGRA tests were implemented most commonly; 44/93 (47.3%) and 42/93 (45.2%) of geographical areas reported using QuantiFERON and T.SPOT tests respectively. Other screening methods or combinations of tests were utilised infrequently.

### **Adherence to national guidance**

Only 33/93 (35.5%) and 6/93 (6.5%) reported complete adherence to BHIVA and NICE guidelines, respectively. No geographical area reported using any non-UK guidelines.

### **Multifactorial reasons for not screening**

Of the geographical areas not offering screening, 31/69 (45%) believed their cohort was at low risk of latent TB infection. 20/69 (29%) cited a lack of confidence in the existing guidelines. 12/69 (17.4%) reported that the tests were too expensive, with 10/69 (14.5%) and 8/69 (11.6%) reporting unavailability of T.SPOT TB and QuantiFERON Gold In-Tube test (or other version) respectively. A few areas cited reasons such as wanting a cost-effectiveness analysis, concern over chemoprophylaxis efficacy, toxicity/drug-drug interactions, and conflicting local advice.

### **Management of LTBI**

Eighty eight of the 93 (94.6%) geographical areas undertaking LTBI screening offer chemoprophylaxis. The most common regimens reported were six months isoniazid (62/88, 70.5%), three months combined isoniazid/rifampicin (49/88, 55.7%), nine months isoniazid (5/88, 5.7%), and combined rifampicin/isoniazid/ethambutol (1/88, 1.1%).

### **Future intention to offer LTBI screening and treatment**

Of the 69 geographical areas not currently offering LTBI screening, 22 (31.9%) indicated a future intention to do so.

Full details of the results are available in the supplementary information.

## **DISCUSSION**

This national evaluation, covering over 90% of HIV positive adults in the UK, is the first to evaluate LTBI screening in this population. It reveals that screening practices are highly heterogeneous in terms of the screening criteria and the tests utilised, and often deviate from published national guidance, although these are themselves non-congruent. Additionally, screening policy was not dependent on the local burden of HIV/TB.

Most cases of active tuberculosis in the UK occur through the reactivation of LTBI in foreign-born individuals. Identification, and treatment of LTBI in high-risk populations (such as those with HIV infection) in the context of a low-burden TB setting such as the UK, where there is relatively little ongoing exposure to *Mycobacterium tuberculosis*, has the potential to augment TB control and prevent morbidity and mortality. However, our work indicates that despite two national guidelines, a relatively low proportion (57.4%) of areas in the UK currently perform any kind of systematic LTBI screening, although a further 14% have expressed a future intention to do so.



Interestingly, the most commonly reported explanation for not offering LTBI screening was a perception that the cohort was at low risk of TB infection, although a quarter of geographical areas not offering screening, have high HIV prevalence/TB incidence.

A lack of confidence in the published guidance, and a view that the current guidelines are too complex were also cited. Although not explicitly stated by the respondents, having two different published guidelines on the same topic may well cause confusion and uncertainty amongst clinicians. Unavailability or high cost of screening tests was the next most reported explanation, raising questions about equitable resource allocation.

Although observational, epidemiological cohort data supports antiretroviral use with wider LTBI screening in HIV positive individuals to prevent active TB, there is an urgent need to prospectively assess which individuals to offer screening to, the optimal screening strategy and the cost-effectiveness of screening in an era of widespread antiretroviral therapy use, thereby informing future national guidance.

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Please see the Supplementary information for a full list of those responding to the evaluation of practice questionnaire.

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